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Posttreatment Changes in *Escherichia coli* Antimicrobial Susceptibility Rates among Diarrheic Patients Treated with Ciprofloxacin

Shannon D. Putnam,[1]* John W. Sanders,[2] David R. Tribble,[3] David R. Rockabrand,[1] Mark S. Riddle,[1] Patrick J. Rozmajzl,[1] and Robert W. Frenck[1]

Naval Medical Research Unit 2, Jakarta, Indonesia[1]; Naval Medical Research Unit 3, Cairo, Egypt[2]; and Naval Medical Research Center, Silver Spring, Maryland[3]

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Changes in antimicrobial resistance of *Escherichia coli* among deployed U.S. military personnel being treated for diarrhea were evaluated. Stool samples were collected pretreatment and on days 7, 14, and 28 posttreatment. Resistance to ciprofloxacin was noted in 13.3% of baseline specimens, and rates of resistance against multiple antibiotics increased dramatically from baseline to day 7 and then tapered off to return to pretreatment levels by day 28, except for ciprofloxacin, suggesting that population accumulative usage of fluoroquinolones may result in an incremental increase in resistance rates.

Deployed military personnel who develop traveler's diarrhea are often prescribed antibiotics to minimize time lost from work (1). The widespread use of antibiotics among military personnel raises the concern of increased antibiotic resistance (8).

From May to September 2002, we conducted a clinic-based diarrhea case series study among deployed U.S. military personnel assigned to Incirlik Air Base, Turkey, where diarrhea occurs commonly and is frequently treated with ciprofloxacin (12). All personnel presenting to the clinic with diarrhea, as previously defined (19), were asked to provide a stool specimen (baseline). After clinical evaluation and treatment, volunteers were instructed to return for reevaluation and specimen collection 7, 14, and 28 days posttherapy. Personnel were excluded if they had received antibiotics within 72 h of presentation (excluding malaria prophylaxis with either doxycycline or mefloquine) or if they had chronic or persistent diarrhea (>14 days) with onset of symptoms preceding deployment.

Stool samples collected at baseline and 7 days were cultured for routine bacterial enteropathogens using standard techniques (4, 6, 13, 21). In addition, five *Escherichia coli* colonies were randomly selected and tested for antimicrobial susceptibility by Kirby-Bauer disk diffusion (3), and NCCLS susceptibility breakpoints were employed (13a). Stool specimens collected on days 14 and 28 were frozen at −70°C and tested approximately 1 year later (100% recovery).

For categorical analysis, either Pearson's chi-square or Fisher's exact test was used; two-tailed statistical significance was set at 0.05. The study was approved and performed in accordance with the ethical standards of the Institutional Review Board of U.S. Naval Medical Research Unit 3 under work unit number 6000.RAD1.D.E0301.

A total of 202 volunteers, predominantly male (89%), median age of 33 years (interquartile range, 26 to 39), who had been in Turkey for a median of 26 days (interquartile range, 13 to 53), were enrolled. Most (94%) patients were empirically treated with ciprofloxacin. Large increases in the resistance rates of each antimicrobial tested were noted in the *E. coli* isolated from stool samples 7 days after treatment (Table 1). Rates of antimicrobial resistance were still elevated compared to baseline in the *E. coli* isolated from patients 14 days after therapy, but values had begun to decrease from day 7 rates (Table 1). With the exception of ciprofloxacin, by day 28, antimicrobial susceptibility neared the baseline rates for all antibiotics tested (Table 1). *E. coli* isolated from stool samples on day 28 still had increased rates of resistance to ciprofloxacin which were nearly double the pretreatment resistance rates (22.3% versus 13.3%, day 28 versus day 0, respectively) ($P < 0.0001$).

In this study, three notable findings concerning antimicrobial resistance in *E. coli* isolates were observed. First, the baseline ciprofloxacin resistance rate was unexpectedly high (13.3%). Since a recent report from Turkey found 10% ciprofloxacin resistance (20), it is possible that our population acquired local bowel flora with ciprofloxacin-resistant strains of *E. coli*. However, we were unable to obtain local antibiograms for comparative studies.

The second notable finding was a significant rise in day 7 posttherapy resistance rates for all antibiotics tested. This is consistent with other studies (7, 14, 18). Unlike other studies, the present project was able to longitudinally evaluate the rates of antimicrobial resistance and by day 28, resistance rates had returned to pretreatment levels for most antimicrobials. A similar pattern of rapid increase of resistance to all antimicrobials tested suggests either a nonspecific mechanism or the appearance of multiple resistance mechanisms. It is possible that ciprofloxacin selected and expanded a subpopulation of resistant *E. coli* (2, 11).

The third finding was that the ciprofloxacin resistance level did not return to baseline by day 28, although it was trending in that direction (Table 1). Given the high baseline rates of resistance found on the base, it raises the concern that resistance rates are being driven up as a direct consequence of antibiotic use for the empirical treatment of diarrhea.

Previously studies have shown that increased rates of cipro-

* Corresponding author. Mailing address: U.S. Embassy Jakarta, NAMRU2 Box 8132, FPO AP 96520. Phone: 62 21 421 4457, ext. 1126. Fax: 62 21 420 7854. E-mail: Putnam@namru2.org.

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TABLE 1. Comparison of baseline and posttreatment antimicrobial resistance rates for all cases[a]

Drug(s)	% of isolates[b] resistant			
	Day 0	Day 7	Day 14	Day 28
Ciprofloxacin	13.3	68.9	53.3	22.3
Ampicillin	45.7	69.7	65.0	49.3
SXT[c]	36.4	65.4	49.5	32.0
Tetracycline	47.4	68.1	61.7	45.0
Chloramphenicol	16.1	37.6	25.6	17.7

[a] All patients were prescribed ciprofloxacin (500 mg twice a day for 3 days).
[b] Number of isolates (number of cases): day 0, 952 (188); day 7, 508 (99); day 14, 465 (93); day 28, 485 (97). Multiple colonies were picked from each case.
[c] SXT, sulfamethoxazole-trimethoprim.

floxacin resistance were associated with increased use of fluoroquinolones (10, 15, 17). It has been hypothesized that this increase is due to the emergence of resistant organisms from the gastrointestinal tract following selective pressure (17). Most prior studies evaluating the emergence of fluoroquinolone-resistant organisms from the gastrointestinal tract following the use of fluoroquinolones have found it to be relatively rare (5, 9, 16). However, Richard et al. (17) found 40% of internal medicine ward patients who received a fluoroquinolone acquired resistant organisms.

Although the present study demonstrated that treatment of traveler's diarrhea with ciprofloxacin substantially increases the antimicrobial resistance rates for multiple antibiotics, those rates appear to return to pretreatment levels within a month. The near normalization of susceptibility by day 28 may suggest that the impact of antibiotic use has little effect on the community antimicrobial resistance levels. However, in the context of frequent antibiotic usage in a relatively small, contained community such as a deployed military unit, the prolonged ciprofloxacin resistance rates may have contributed to a steady increase in community baseline fluoroquinolone resistance rates, which could result in future clinical complications and added financial costs. As the empirical treatment of traveler's diarrhea with antibiotics has been shown to result in a rapid cure and return to duty, it is likely that this practice will continue. Therefore, additional work needs to be performed to characterize the potential for creating antibiotic resistance. Genetic characterization may help clarify the changes that occur in enteric flora experiencing antibiotic pressure.

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This research has been conducted in compliance with all federal regulations governing the protection of human subjects in research.

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